Pulmonary arterial hypertension: Newer treatments are improving outcomes

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Practice recommendations

- Echocardiography is useful for screening high-risk patients (SOR: **A**).

- The New York Heart Association classification of dyspnea has been modified by the World Health Organization to categorize pulmonary hypertension by the severity of symptoms, which, unlike pulmonary arterial pressure, correlates well with survival (SOR: **A**).

- Calcium channel blockers are useful only for patients who respond to vasodilator testing in a cardiac catheterization laboratory (SOR: **A**).

- Therapeutic modalities now include parenteral prostanoids, oral endothelin receptor antagonists, PDE5 inhibitors, and lung transplantation (SOR: **A**; for PDE5 inhibitors, SOR: **B**)

- Early referral to expert centers is crucial to patient survival (SOR: **B**).

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Recent progress in understanding the pathobiology of pulmonary arterial hypertension (PAH) has been tremendous, and treatment options have multiplied to include prostanoids, endothelin antagonists, phosphodiesterase-5 inhibitors, anticoagulants, and surgical options such as lung transplantation and atrial septostomy.

Although idiopathic pulmonary arterial hypertension, formerly called "primary," is rare, other forms of PAH and associated cor pulmonale are more prevalent than conventionally believed. It is a life-threatening disease best managed within a diagnostic framework such as the one reviewed here with a treatment algorithm and recommendations from evidence-based guidelines.

■ PATIENTS MOST LIKELY TO EXPERIENCE PULMONARY ARTERIAL HYPERTENSION

Pulmonary arterial hypertension may be *idiopathic* and sporadic (IPAH), *familial* (FPAH), or *associated with* (APAH) connective tissue diseases, congenital systemic to pulmonary shunts, portal hypertension, HIV, drugs including anorexigens or cocaine, and other disorders (**Table 1**).[1]

Annually, 1 to 2 cases of IPAH occur per million population.[2] The mean age at diagnosis is 36 years, and women are affected more often than men by a ratio of 1.7–3.5:1. This female predominance has also been noted in PAH associated with scleroderma,[3] congenital heart disease,[4] and anorexigen-induced PAH.[5] The incidence among

TABLE 1

The 2003 Venice clinical classification of pulmonary hypertension*

1. Pulmonary Arterial Hypertension
    1.1. Idiopathic (IPAH)
    1.2. Familial (FPAH)
    1.3. Associated with (APAH):
        1.3.1. Collagen vascular disease
        1.3.2. Congenital systemic-to-pulmonary shunts
        1.3.3. Portal hypertension
        1.3.4. HIV infection
        1.3.5. Drugs and toxins
        1.3.6. Others (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
    1.4. Associated with significant venous or capillary involvement
        1.4.1. Pulmonary veno-occlusive disease (PVOD)
        1.4.2. Pulmonary capillary hemangiomatosis (PCH)
    1.5. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left heart disease
    2.1. Left-sided atrial or ventricular heart disease
    2.2. Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
    3.1. Chronic obstructive pulmonary disease
    3.2. Interstitial lung disease
    3.3. Sleep-disordered breathing
    3.4. Alveolar hypoventilation disorders
    3.5. Chronic exposure to high altitude
    3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
    4.1. Thromboembolic obstruction of proximal pulmonary arteries
    4.2. Thromboembolic obstruction of distal pulmonary arteries
    4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

5. Miscellaneous
    Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

*Classification does not include pulmonary hypertension due to end-stage renal disease.[13]

users of anorexigens such as fenfluramine, dexfenfluramine, and aminorex is estimated to be 25 to 50 per million per year.[2]

The prevalence of portopulmonary hypertension is about 0.73% in cirrhosis.[6] In scleroderma, the incidence is between 6% to 60%,[7,8] while in systemic lupus erythematosus (SLE) it is reported to be 4% to 14%.[9,10] In one study, 21% of rheumatoid arthritis patients without underlying cardiopulmonary disease had mild pulmonary hypertension (PH).[11] PAH occurs in about 0.5% of patients with HIV infection.[12]

Included in the "others" group are hemoglobinopathies such as sickle cell anemia. This classification does not include PH due to end-stage renal disease, a recently described entity in

Ortner's syndrome

Ortner's syndrome was first described in 1897. The commonest cause has been thought to be mitral valve stenosis or prolapse leading to left atrial dilatation that compresses the recurrent laryngeal nerve as it hooks around the aorta next to the ligamentum arteriosum and courses up in the groove between the trachea and esophagus. However, other vascular structures can also compress this nerve, including a thoracic aortic aneurysm, or a dilated pulmonary artery from pulmonary arterial hypertension.

ILLUSTRATION BY JENNIFER FAIRMAN

Thyroid cartilage
Recurrent laryngeal nerve
Trachea
Vagus nerve
Recurrent laryngeal nerve
Ligamentum arteriosum
Pulmonary artery
Pulmonary veins
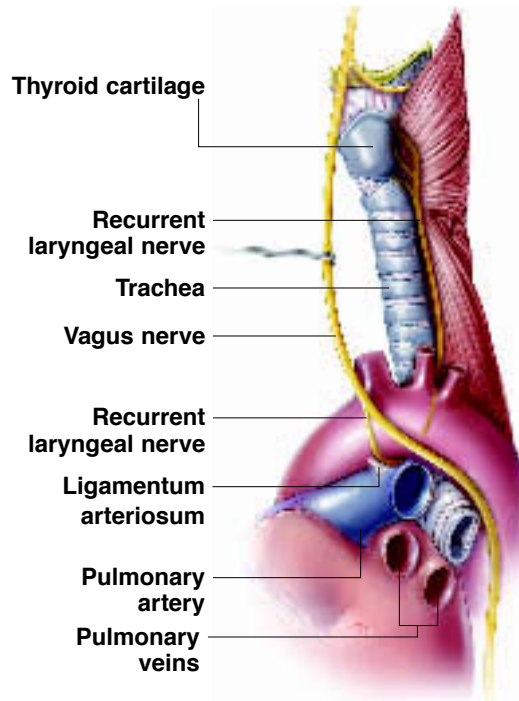
patients with arteriovenous fistulae that portends a poorer prognosis.[13] PH was present in a surprising 40% of hemodialysis patients.

■ CLINICAL PRESENTATION

Pulmonary arterial hypertension manifests the following symptoms and signs:

Symptoms
- Progressive onset of exertional dyspnea (60%)[14]
- Chest pain or discomfort (17%)
- Palpitations (5%)
- Dizziness and light-headedness. There may be a history of near-syncope or syncope (13%)
- Fatigue (19%)
- Ortner's syndrome: hoarseness from compression of left recurrent laryngeal nerve by enlarged pulmonary artery (<1%) (See **Ortner's syndrome**)
- Raynaud's phenomenon (10%)
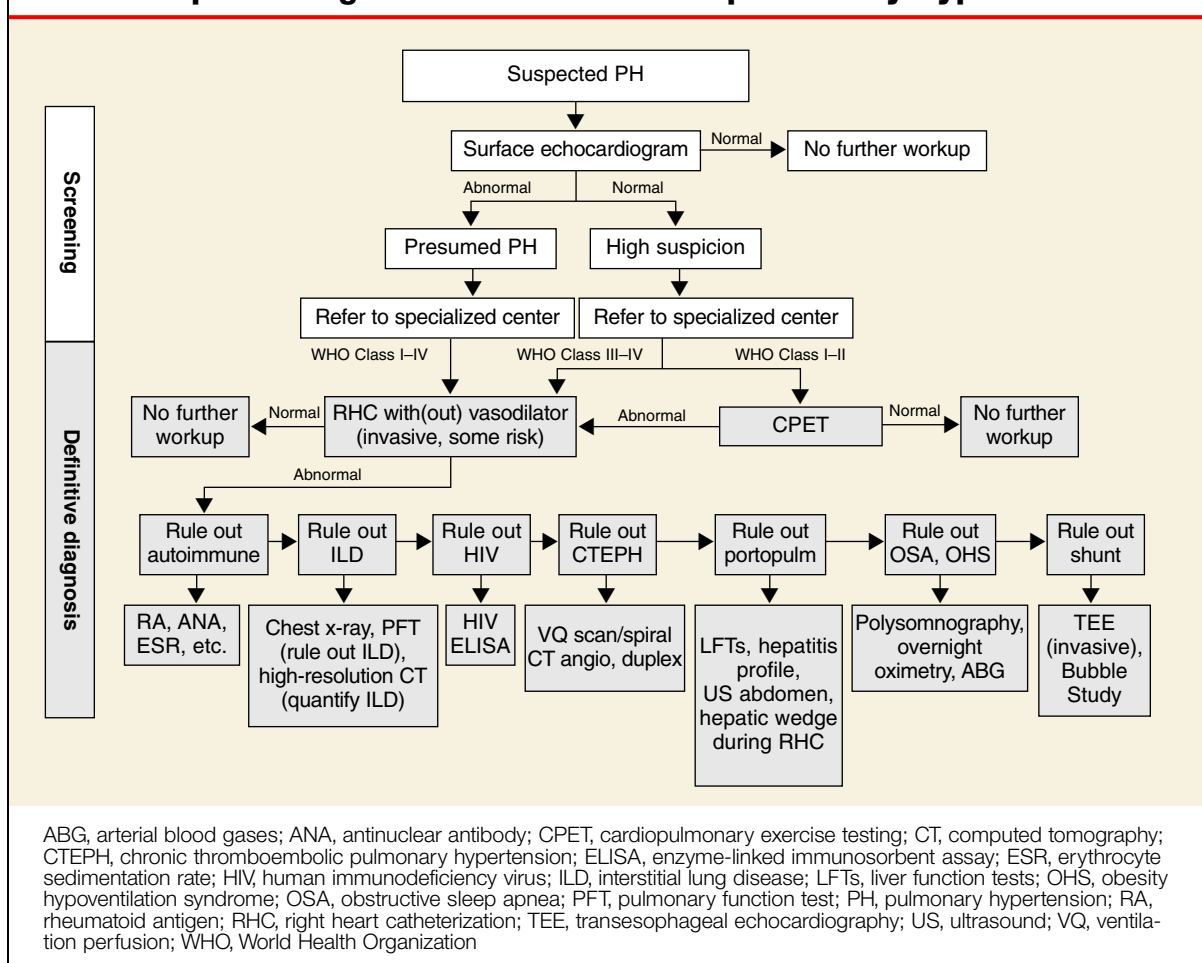
Signs
- Loud P2 (93%)
- Tricuspid regurgitation murmur (40%)
- Right ventricular heave
- Jugular venous distention with a prominent "a" wave
- Graham Steell's murmur: diastolic pulmonary regurgitation murmur best heard at upper left sternal border (13%)
- Signs of right heart failure including S3 gallop, "v" wave in central venous pressure tracing, hepato-jugular reflux, peripheral edema, and ascites
- Cutaneous telangiectasia.

■ AN EFFICIENT DIAGNOSTIC FRAMEWORK

Proceed with a stepwise assessment (**Figure 1**) of any patient exhibiting signs or symptoms suggestive of PH, particularly if there is an associated underlying condition or suggestive imaging study. Echocardiography (ECG) is usually the first test ordered, to detect thickening of the right ventricle or regurgitation of blood into the right atrium. ECG is neither sensitive nor specific for PAH. Not

FIGURE 1

Conceptual diagnostic framework for pulmonary hypertension

ABG, arterial blood gases; ANA, antinuclear antibody; CPET, cardiopulmonary exercise testing; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; ILD, interstitial lung disease; LFTs, liver function tests; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PFT, pulmonary function test; PH, pulmonary hypertension; RA, rheumatoid antigen; RHC, right heart catheterization; TEE, transesophageal echocardiography; US, ultrasound; VQ, ventilation-perfusion; WHO, World Health Organization

every patient will require the full work-up outlined in **Figure 1**. The sequence and extent of testing depend on the clinical scenario. Cardiac catheterization is sometimes the last procedure, given its risks of invasiveness. A surface echocardiogram has a sensitivity of 79% to 100% and specificity of 60% to 98% for detecting PAH.[15]

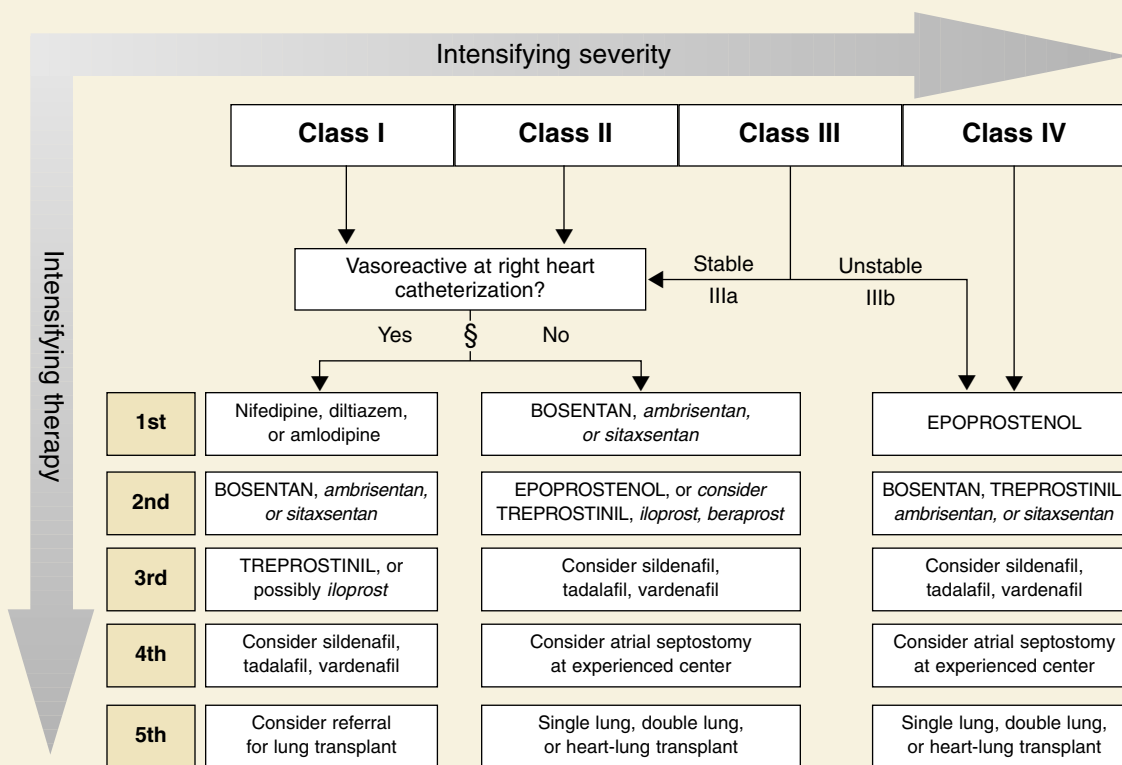### Functional assessment most important

Mean blood pressure above 25 mm Hg at rest or *systolic* pressure over 40 mm Hg in the pulmonary circulation constitutes pulmonary hypertension (see **Pulmonary hypertension criteria**). However, the correlation of mean pulmonary arterial pressure to disease severity is not straightforward.[16]

Higher pulmonary artery pressure may portend *better* survival. The severity of pulmonary arterial hypertension is better determined by functional assessment. The New York Heart Association (NYHA) classification of dyspnea has been modified by the World Health Organization (WHO) to categorize PH by the severity of symptoms, which, unlike pulmonary arterial pressure, correlates well with survival. Even with epoprostenol treatment, functional class III patients have a survival of 60% at 7 years compared with less than 20% for class IV.[17]

Class I: Patients with pulmonary hypertension but without limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Treatment algorithm for pulmonary arterial hypertension

Intensifying severity

Intensifying therapy

	Class I	Class II	Class III	Class IV

Vasoreactive at right heart catheterization?

Stable IIIa

Unstable IIIb

Yes § No

1st	Nifedipine, diltiazem, or amlodipine	BOSENTAN, *ambrisentan, or sitaxsentan*	EPOPROSTENOL
2nd	BOSENTAN, *ambrisentan, or sitaxsentan*	EPOPROSTENOL, or *consider* TREPROSTINIL, *iloprost, beraprost*	BOSENTAN, TREPROSTINIL, *ambrisentan, or sitaxsentan*
3rd	TREPROSTINIL, or possibly *iloprost*	Consider sildenafil, tadalafil, vardenafil	Consider sildenafil, tadalafil, vardenafil
4th	Consider sildenafil, tadalafil, vardenafil	Consider atrial septostomy at experienced center	Consider atrial septostomy at experienced center
5th	Consider referral for lung transplant	Single lung, double lung, or heart-lung transplant	Single lung, double lung, or heart-lung transplant

Agents that are not FDA-approved are listed in italics, and their use should be considered experimental at this time. Drugs specifically approved for PAH are listed in capitals. There is an increasing trend towards combination therapy—ie, adding second-line agents rather than replacing the first-line therapy.

§ = Criteria for vasoreactivity

Reduction in mean PA pressure by at least 10 mm Hg, absolute value less than 40 mm Hg, and increased or unchanged CO.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea or fatigue may be present even at rest. Discomfort increases with any physical activity.

■ CHOOSING FROM AMONG IMPROVED THERAPEUTIC OPTIONS

Main therapeutic goals are to prevent or reverse vasoconstriction, inhibit smooth muscle proliferation, impede thrombosis, and thereby reduce right ventricular failure. Newer pharmacologic agents have improved outcomes for patients and may even obviate the need for surgery. Treating the underlying cause of PH may be helpful, such as

TABLE 2

Treatment options for pulmonary arterial hypertension

	Medication	SOR*	Route	Adverse effects	Cost†
Prostanoids	**Epoprostenol**	A	Intravenous	Line-related sepsis and thrombosis, jaw pain, fatal arrhythmia with sudden interruption	$$$$
	Treprostinil	B	Subcutaneous	Site pain (85%), jaw pain	$$$$
	Iloprost	B	Inhaled	Short half-life with intermittent benefit	
Endothelin antagonists	**Bosentan**	A	Oral	Hepatotoxicity, teratogenicity, fluid retention	$$$
	Sitaxsentan	B			
	Ambrisentan	C			
PDE5 inhibitors	**Sildenafil**	B	Oral	Short half-life, retinopathy	
	Vardenafil	I		Short half-life	$$
	Tadalafil	I			
Surgical options	**Lung transplant**	C		Complicated procedure, lifelong immunosuppression	$$$$
	Atrial septostomy	C		Invasive procedure, hypoxemia	$$
Conventional therapy	**Diuretics**	C		Electrolyte imbalance, dehydration, etc	$
	Digoxin	C		Higher mortality with high serum level	$
	Warfarin	C		Bleeding diathesis, dosing difficult in liver disease	$
	Calcium channel blockers	C		Harmful in vasodilator nonresponders	$

Note: The level of evidence implied by the strength of recommendation must not be confused with level of efficacy. Medications not currently approved by the FDA for any indication are listed in italics. Only epoprostenol, bosentan, and treprostinil are approved specifically for pulmonary arterial hypertension.

*SOR = strength of recommendation. A = Data derived from multiple randomized clinical trials or meta-analyses; B = Data derived from single randomized clinical trials or from multiple randomized clinical trials with heterogeneous results; C = Data derived from small randomized studies or consensus opinion of experts;[59] I = indeterminate, no data available, theoretical basis only. See "Evidence-based medicine terms" on page 995.

immunosuppression for SLE[18] or positive pressure in sleep-disordered breathing.[19] **Table 2** outlines therapeutic options, and **Figure 2** presents a strategy for applying these options.

Conventional therapies

Calcium channel blockers. Calcium channel blockers (CCBs) are useful only for PAH patients who respond to vasodilator testing in a cardiac catheterization laboratory (SOR: **B**). Criteria for vasoresponsiveness have changed and it is now generally agreed that the mean PA pressure must fall by at least 10 mm Hg to ≤ 40 mm Hg with increased or unchanged cardiac output. CCB use for nonresponders leads to higher morbidity and mortality.[20]

Digoxin. In *left* ventricular failure, digoxin relieves symptoms, but without mortality benefit (SOR: **A**).[21] Only 1 study has shown a

hemodynamic benefit in PAH in the intensive-care setting.[22] Therefore, experts do not agree that digoxin is useful in right ventricular failure from PAH. Digoxin may be warranted in the presence of concomitant left ventricular dysfunction or digoxin-responsive arrhythmias.

Warfarin. Two retrospective studies have shown a decrease in mortality with warfarin in PAH.[23,24] There is no consensus, though, on the degree of anticoagulation, with recommendations of INR ranging from 1.5 to 4.0.

Diuretics. Judicious use of diuretics is recommended in PAH. Loop diuretics, thiazides, and spironolactone are commonly titrated to achieve symptomatic relief.

Ambulatory oxygen therapy. This option is indicated for resting and exercise-induced hypoxia. Experts usually recommend titration to achieve a PO_2 >60 mm Hg.

Prostanoids: Epoprostenol, treprostinil, iloprost

Prostanoids cause vasodilation, inhibit platelet aggregation, prevent smooth muscle proliferation, decrease inflammation, and increase cardiac output.[25] Epoprostenol improves exercise tolerance, hemodynamics and quality of life in patients with IPAH and PAH secondary to scleroderma (SOR: **A**).[3,26] Treprostinil and iloprost show similar benefits. A survival advantage has only been shown for epoprostenol and treprostinil.[27] Epoprostenol is useful in both vasodilator "responders" and "non-responders."[28]

Administration. Epoprostenol is administered with a central venous catheter. Usual starting dose is 2 ng/kg/min or higher with increase by 1 ng/kg/min every 1 to 2 weeks until the desired clinical improvement is manifested, or side effects preclude dose escalation.[29]

Treprostinil is given subcutaneously and is under investigation as an intravenous agent. The optimal dose for treprostinil is 13.8 ng/kg/min and above.[30]

Iloprost is delivered via inhalation, although it has also been used intravenously. Iloprost is not approved by the Food and Drug Administration

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Pulmonary hypertension criteria

Pulmonary hypertension (PH) refers to elevated blood pressure within the pulmonary circulation. The term **pulmonary arterial hypertension** (PAH) encompasses a spectrum of disorders that cause PH with a common histopathology and pathobiology.[56] The hallmark histopathologic lesion is plexogenic pulmonary arteriopathy.[57]

Normal *mean* pulmonary artery (PA) pressure is 12 to 16 mm Hg. PH is defined as a mean PA pressure greater than 25 mm Hg at rest, or greater than 30 mm Hg on exertion. Alternatively, *systolic* PA pressure greater than 40 mm Hg is also considered to be PH.[58] Pulmonary arterial hypertension (PAH) is defined as a mean PA pressure greater than 25 mm Hg at rest (or 30 mm Hg with exercise), with a concomitant pulmonary capillary wedge pressure less than 15 mm Hg and a pulmonary vascular resistance (PVR) greater than 3 Woods units[14] or 240 dyn•sec•cm[–5].

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but is available in clinical trials. Inhaled iloprost is short-lived and only provides intermittent hemodynamic benefit.[31]

Side effects. Side effects include jaw pain, nausea, anorexia, diarrhea, flushing, and headache. With the exception of jaw pain, these side effects are dose-related. The risk of catheter sepsis with epoprostenol is 0.1% to 0.4% per patient-year. More serious side effects include arrhythmia with sudden interruption of drug delivery. Treprostinil causes infusion site pain (85%), necessitating discontinuation in 8% of the patients.

Endothelin receptor antagonists: Bosentan, sitaxsentan, ambrisentan

In the lung parenchyma of patients with PH, expression of endothelin-1, a 21-amino-acid peptide, increases.[32] Higher levels of serum endothelin-1 correlate directly with severity of PH

and poorer outcomes.[33] Endothelin-1 mediates vasoconstriction and smooth muscle proliferation primarily through endothelin type A (ET_A) receptors and vasodilatation mostly through endothelin type B (ET_B) receptors, although a dynamic relationship exists between the two.[34]

Oral formulation a plus. Bosentan is the only endothelin antagonist currently approved by the FDA. It is a low-molecular-weight, nonpeptide, competitive, dual receptor antagonist. Sitaxsentan and ambrisentan are available in clinical trials only. They are ET_A-selective with the premise that sparing the ET_B receptor, which is responsible for pulmonary vasodilation, will lead to better clinical outcomes. All these compounds can be given orally, a major advantage over prostanoids.

Bosentan improves exercise capacity, hemodynamics, symptoms, and time to clinical worsening.[35,36] Patients studied in bosentan trials had NYHA class III or IV dyspnea due to IPAH, APAH due to scleroderma, and others. Bosentan is not approved by the FDA for functional class II patients, but has been used for such patients.

Indicated for milder PAH. Bosentan outcome data were presented at the American Thoracic Society Meeting (2003) but have not been published so far. At 3 years, 86% of patients were still alive when only 48% were expected based on historical data from the NIH registry.[37] Epoprostenol survival at 3 years is about 63%.[16,17] However, only patients with milder PAH receive bosentan, while the more seriously ill ones require prostanoids. This selection may explain the survival difference.

Administration. Recommended starting dose of bosentan is 62.5 mg twice daily for 4 weeks. It is then increased to 125 mg twice daily if there is no elevation of aminotransferases. Bosentan is now known to be safe in children.[38] Ambrisentan and sitaxsentan should to be available in 2005 or later.

Side effects. The most common side effect of bosentan is hepatic aminotransferase elevation (9% of patients), usually occurring within 16 weeks (90%). All elevations have resolved upon drug withdrawal (97% within 8 weeks). The FDA mandates monthly monitoring of aminotrans-

ferase for bosentan. Furthermore, bosentan is teratogenic[39] and absolutely contraindicated in pregnancy. There may be significant fluid retention. Sitaxsentan and ambrisentan have similar side effects and their eventual clinical use is expected to require similar monitoring.

Phosphodiesterase-5 inhibitors: Sildenafil, vardenafil, tadalafil

Phosphodiesterases (PDEs) are a group of isoenzymes widely distributed in various organs. PDE5 is found in the corpus cavernosum, pulmonary vasculature, muscle, and platelets.

Use for PAH off-label. Sildenafil, vardenafil, and tadalafil are cyclic guanosine monophosphate-specific PDE5 inhibitors with potent, selective pulmonary vasodilatory and antiplatelet effects. Sildenafil and vardenafil have relatively short half-lives (4–6 hours). Tadalafil has a longer half-life (17.5 hours) with potential for once-daily administration. All these compounds are only available orally. The FDA has approved these for erectile dysfunction only, but they have been used off-label.

A phase III study of sildenafil in PAH has been completed, but has not been published. One randomized study has shown clinical efficacy.[40] Small series have also shown clinical improvement.[41,42]

Due to their short half-lives, sildenafil and vardenafil require multidose regimens, with potential for noncompliance leading to rebound pulmonary vasoconstriction. Retinopathy at high dose, from inhibition of PDE6, remains a concern for sildenafil.[43] Priapism has not been reported in the PAH population so far, but may be a relevant consideration in sickle cell anemia.

Lung transplantation

Lung transplantation should be considered if functional class II is not achieved despite optimal medical therapy.[44] Improved medical therapy has decreased the need for this surgical option, lengthened the time to transplantation, or even eliminated the requirement altogether.[45] The 5-year survival of patients on epoprostenol is comparable with, or better than, that with lung transplant.[46] Patient

selection and early referral for transplantation are crucial to success in this process. Published international guidelines help guide this process.[47] In general, PAH patients in WHO functional class II, III, or IV should be medically treated. Concurrently, referral for transplantation should be considered, even before there are signs that functional class I or II cannot be achieved. This is because transplant evaluation is a fairly lengthy process and it is not unusual for patients to die while on the long waiting list. If medical therapy is successful, the patient can be inactivated. In case medical therapy begins to fail subsequently, listing can be reactivated.

Lung transplantation remains the surgical treatment of choice for refractory PAH. Heart-lung transplants tend to be reserved for patients with structural cardiac abnormalities. Single lung transplantation has the advantages of less complex surgery and more efficient use of harvested organs to benefit more patients, thereby leading to shorter waiting periods. However, most transplant centers in the US prefer double lung transplantation, mainly because there is greater pulmonary reserve should the patient sustain rejection or infection.[48]

The operative mortality range is between 16% to 29%.[48] The 1-year survival rate after lung transplantation (single as well as double) is approximately 70% to 75%, 2-year survival is 50% to 60%, and 5-year survival is 40% to 45%.[49] The International Society of Heart and Lung Transplantation database shows that overall survival for both single and double lung transplantation is nearly equal up to 3 years postsurgery. After that, there is a significant survival advantage for double lung transplant.[50] Although several studies have documented a significant improvement in the quality of life after transplantation for PH, cost-effectiveness has not yet been addressed.

Balloon atrial septostomy

Balloon atrial septostomy reduces strain on the right ventricle and improves cardiac output. Its use is limited by systemic hypoxemia caused by the right-to-left shunt and perioperative morbidity. It may be used as a bridge procedure while awaiting lung transplantation.[51] Functional improvement has been demonstrated in a small series.[52] Patient selection, improvement in hemodynamics, and clinical outcomes vary from center to center.[53,54] It is likely that patient selection, technique, and experience influence the outcome considerably. This procedure should only be performed in experienced centers on carefully selected patients.

Combination therapy increasingly used

There are no prospective data on combination therapy for PAH. Whether combination therapy has an additive, synergistic, or even antagonistic effect is uncertain. However, there is pathophysiologic rationale for this approach, especially in therapeutic failure following monotherapy. Addition of sildenafil to epoprostenol reduces PA pressure and PVR without hypotension or desaturation.[42] When iloprost failed as monotherapy for 14 patients with PAH, addition of sildenafil reversed clinical deterioration, increased functional capacity, and yielded favorable hemodynamics at 3 months, with sustained efficacy up to 12 months.[55] There are no data showing whether sildenafil will have synergistic benefits with bosentan. Despite lack of evidence, combination therapy has been used increasingly in clinical practice.

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DRUG BRAND NAMES

Amlodipine • Norvasc
Bosentan • Tracleer
Digoxin • Lanoxin
Epoprostenol • Flolan
Iloprost • Ventavis
Nifedipine • Adalat, Procardia
Sildenafil • Viagra
Sitaxsentan • Thelin
Spironolactone • Aldactone
Tadalafil • Cialis
Treprostinil • Remodulin
Vardenafil • Levitra
Warfarin • Coumadin